

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 601

[Docket No. 99N-1852]

Postmarketing Studies for Approved Human Drug and Licensed Biological Products; Status Reports

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

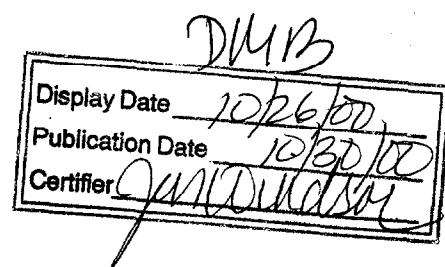
SUMMARY: The Food and Drug Administration (FDA) is revising the requirements for annual postmarketing status reports for approved human drug and biological products, and is requiring applicants to submit annual status reports for certain postmarketing studies of licensed biological products. This rule describes the types of postmarketing studies covered by these status reports, the information to be included in the reports, and the type of information that FDA would consider appropriate for public disclosure. This action will implement the Food and Drug Administration Modernization Act of 1997 (FDAMA).

DATES: This rule is effective *[insert date 120 days after date of publication in the Federal Register]*.

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SUPPLEMENTARY INFORMATION:



NFR 1

I. Background

A. Statutory Requirements

Section 130(a) of FDAMA (Public Law 105–115) amended the Federal Food, Drug, and Cosmetic Act (the act) by adding a new provision on reports of postmarketing studies (section 506B of the act (21 U.S.C. 356b)). Section 506B of the act provides FDA with additional authority for monitoring the progress of postmarketing studies that applicants have made a commitment to conduct and requires the agency to make publicly available information that pertains to the status of these studies. The following summary describes the obligations of applicants and of FDA under section 506B of the act.

1. Submission of Annual Reports to FDA Under Section 506B of the Act

Any applicant that has committed to conduct a postmarketing study for a drug or biological product that is approved for marketing must submit to FDA a report on the progress of the study or the reasons for the failure of the applicant to conduct the study. The applicant must submit the report within a year after the approval of the product and annually thereafter on the anniversary of the product's U.S. approval until the study is completed or terminated. This provision applies to commitments for postmarketing studies that were made on or after enactment of FDAMA, as well as commitments made before enactment of FDAMA.

2. Special One-Time Reporting Requirement Under Section 506B of the Act

An applicant must submit an initial report to FDA for study commitments made before November 21, 1997, within 6 months after the effective date of the final rule. Subsequent to the initial report, an applicant must submit an annual report to the agency on the anniversary of the product's U.S. approval. For those applicants required to submit an annual report 7 to 12 months after the effective date of the final rule, the submission of the initial report to FDA within 6 months after the effective date of the final rule is an additional one-time burden.

3. FDA Obligations Under Section 506B(c) of the Act

FDA must develop and publish annually in the **Federal Register** a report on the status of postmarketing study commitments.

4. FDA Obligation Under FDAMA (Section 130(b))

FDA must submit a specific report to Congress by October 1, 2001, that contains the following:

1. A summary of the status reports submitted under section 506B of the act;
2. An evaluation of the performance of applicants in fulfilling their commitments to conduct postmarketing studies under this provision;
3. FDA's timeliness in reviewing these postmarketing studies; and
4. Any legislative recommendations regarding postmarketing studies.

B. Proposed Rule

FDA published a proposed rule in the **Federal Register** of December 1, 1999 (64 FR 67207), that would revise the requirements for annual postmarketing status reports for drug and biological products, and that would require applicants to submit annual status reports for certain postmarketing studies of licensed biological products. The proposed rule described the types of postmarketing studies covered by these status reports, the information to be included in the reports, and the type of information that FDA would consider appropriate for public disclosure. The agency proposed this action to implement section 130 of FDAMA. In proposed §§ 314.81(b)(2)(vii) and (b)(2)(viii), and 601.70(b), FDA would require that a status report for a postmarketing study contain the following information:

1. Applicant's name.
2. Product name. This would include the approved product's established/proper name and proprietary name, if applicable.

3. New drug application (NDA) number, abbreviated new drug application (ANDA) number, biologics license application (BLA) reference number, or supplement number for the approved product.

4. Date of product's U.S. approval.

5. Date of postmarketing study commitment.

6. Description of postmarketing study commitment. For clinical studies, this section would include the purpose of the postmarketing study, the patient population addressed by the study, the number of patients and/or subjects to be included in the study, and the indication and dosage(s) that are to be studied. For nonclinical studies, this section would include the type and purpose of the study (e.g., carcinogenicity study to determine effects of chronic dosing).

7. Schedule for conduct, completion, and reporting of the postmarketing study commitment. This section would include projected dates for initiation of the different phases of the study, for completion of the study, and for submission of the final study report to FDA. If the original schedule is revised under section 9 of this status report, the revised schedule would also be reported in this section (i.e., section 7) in the next status report with a note indicating that the schedule has been revised as reported in the previous status report.

8. Current status of the postmarketing study commitment. Applicants would categorize the status of each postmarketing study using one of the following terms that describe the study's status on the U.S. anniversary date of approval of the application or other agreed date:

a. *Pending*. The study has not been initiated (i.e., first patient has not been enrolled).

b. *Ongoing*. The study is proceeding according to, or ahead of, the original schedule described in section 7 of the status report. If a study has been completed but the final study report has not been submitted to FDA, the date the study was completed would be provided.

c. *Delayed*. The study is proceeding but is behind the original schedule described in section 7 of the status report.

d. *Terminated*. The study was ended before completion.

e. *Submitted.* The study has been completed (i.e., last patient finished the protocol) or terminated and a final study report has been submitted to FDA. This category would include the date the final study report was submitted to FDA.

9. Explanation of the study's status. This section would include a brief description of the status of the study, including the number of patients and/or subjects enrolled to date and an explanation of the study's status identified under section 8 of the status report (e.g., delayed due to difficulty in patient accrual, terminated because study would no longer provide useful information, terminated because study is no longer feasible, terminated because of adverse events or other safety issues associated with the use of the product). If the schedule under section 7 of the status report has changed since the last annual report, this section would also include a revised schedule, as well as the reason(s) for the revision.

FDA invited the public to submit written comments on the proposed rule by February 14, 2000, and on the information collection provisions by January 3, 2000. Comments received have been considered and are discussed in section III of this document. No comments were received on the information collection provisions.

C. Availability of Guidance

To help applicants comply with the requirements of this final rule, the agency is developing a guidance for industry entitled "Reports on the Status of Postmarketing Studies—Implementation of section 130 of the Food and Drug Administration Modernization Act of 1997." FDA intends to make a draft of this guidance available shortly after publication of this final rule.

II. Description of the Final Rule

This final rule amends parts 314 and 601 (21 CFR parts 314 and 601) to revise the status reports section of postmarketing annual reports for drug and licensed biological products (§§ 314.81(b)(2)(vii) and 601.28). This final rule also amends part 601 to require applicants with

licensed biological products to submit a separate annual report that describes the status of certain postmarketing studies (§ 601.70). The major provisions of the final rule are summarized below.

Under §§ 314.81(b)(2)(vii) and 601.70(a), the final rule defines postmarketing studies for which status reports must be submitted to FDA under section 506B of the act as those that concern: (1) Clinical safety; (2) clinical efficacy; (3) clinical pharmacology; and (4) nonclinical toxicology studies that are either required by FDA (e.g., accelerated approval clinical benefit studies, pediatric studies) or committed to by the applicant, in writing, at the time of approval of an application or a supplement or after approval of an application or supplement. FDA is including clinical safety and efficacy and clinical pharmacology studies within the scope of this rule because these types of studies provide the most relevant and useful additional information about the risks, benefits, and optimal use of an approved drug or licensed biological product. FDA also is including nonclinical toxicology studies within the scope of this rule, although such studies are not performed on human subjects, because they are important to the further evaluation of the safety of a marketed drug or biological product. For the purpose of this rule, clinical safety and clinical efficacy studies include human epidemiological studies. Clinical pharmacology studies include pharmacokinetic and pharmacodynamic studies.

Under §§ 314.81(b)(2)(vii) and 601.70, the final rule requires applicants to provide status reports to FDA regarding the progress of the postmarketing studies described above. In addition, under § 314.81(b)(2)(viii), applicants with approved NDA's and ANDA's must provide status reports for any postmarketing study not reported under § 314.81(b)(2)(vii) (e.g., chemistry, manufacturing, controls, product stability). These include postmarketing studies performed by, or on behalf of, the applicant on its own initiative. Section 314.81(b)(2)(viii) does not represent a new reporting burden for applicants with approved NDA's or ANDA's because these applicants are currently required to provide status reports on postmarketing studies in annual reports. FDA is not requiring a similar reporting requirement for postmarketing studies of licensed biologicals

in this rule. However, applicants with licensed biological products may voluntarily submit status reports to FDA for postmarketing studies that are not required to be reported under § 601.70.

The agency is committed to harmonizing its reporting requirements for drugs and biologics as much as possible. FDA considered amending its biologics regulations to require the submission of information in postmarketing annual reports currently submitted to the agency by applicants with approved NDA's and ANDA's under § 314.81(b)(2)(i) through (b)(2)(vi). FDA also considered combining postmarketing annual reports required under §§ 601.12(d), 601.28, and proposed 601.70 into a single annual report that would include additional information as required in § 314.81(b)(2)(i) through (b)(2)(vi). However, FDA has determined that requiring such additional information is beyond the scope of this rulemaking, and that it is appropriate, at this time, to harmonize only the drugs and biologics postmarketing annual reporting requirements as they relate to section 506B of the act.

III. Comments on the Proposed Rule and FDA Responses

FDA received seven comments on the proposed rule from representatives of pharmaceutical companies and associations. While most comments agreed that the proposed rule appropriately implements section 130 of FDAMA, many comments expressed concern about what information should be included in the status reports and what information should be disclosed to the public.

A discussion of the comments on the proposed rule and the agency's responses follows.

A. Status Reports

(Comment 1) One comment claimed that the proposed content of status reports exceeds that necessary to determine, as stated in section 130 of FDAMA, "the progress of the study or the reasons for the failure of the sponsor to conduct the study." The comment said that the agency turns the simple reporting requirement contemplated by FDAMA into a potentially complicated and burdensome exercise. For example, the comment noted that applicants must provide detailed information on a postmarketing study commitment regarding the purpose of the study, the patient

population addressed by the study, the indication and dosage(s) that are to be studied, the projected dates for initiation of the different phases of the study and completion of the study, the status of patient accrual, as well as an explanation of the study's status (which would be categorized separately). The comment recommended that the proposed rule be revised to require applicants to simply identify a pertinent postmarketing study commitment and report on its status using a standardized description. The comment added that additional details regarding the postmarketing study commitment should be provided at the discretion of the applicant.

FDA has reviewed the proposed content for status reports and has decided to make several changes. In §§ 314.81(b)(2)(vii)(a)(6) and 601.70(b)(6), the agency is revising the requirements for the "Description of postmarketing study commitment" section of status reports to permit an applicant to determine the type of information that is necessary to identify a postmarketing study commitment. Instead of specifying the elements that would be required to be included in this section, the provision now provides examples of the type of information that applicants may choose to use to describe a postmarketing study commitment. This section, as revised, now reads:

The description must include sufficient information to uniquely describe the study. This information may include the purpose of the study, the type of study, the patient population addressed by the study and the indication(s) and dosage(s) that are to be studied.

The list of examples does not contain "the number of patients and/or subjects to be included in the study." However, an applicant is required to include patient accrual information (by providing the number of patients or subjects enrolled to date and the total planned enrollment) in the section requiring an explanation of the study's status.

The agency recognizes that the extent of information necessary to identify various postmarketing study commitments will vary. In most cases, it will be sufficient to use the language provided in the FDA document describing the postmarketing study commitment (e.g., action letter). In other cases, such as when multiple studies are required to fulfill a postmarketing study commitment, additional information is likely to be needed to describe each of the studies.

In §§ 314.81(b)(2)(vii)(a)(7) and 601.70(b)(7), the agency is revising the “Schedule of conduct, completion and reporting of the postmarketing study commitment” section of the status report to require inclusion of only the information that is most important in determining the progress of a study and to clarify that information. FDA is replacing the phrase “projected dates for initiation of the different phases of the study” with the phrase “actual or projected dates for submission of the study protocol to FDA, completion of patient accrual or initiation of an animal study” and adding “any additional milestones or submissions for which projected dates were specified as part of the commitment.” FDA recognizes study phases may vary depending on the type of study and the study design. Because information on some phases of a study may not be meaningful in establishing study progress, FDA is limiting the information for this section to the projected, or actual, dates for the submission of the study protocol to FDA; for completion of patient accrual into a clinical study or initiation of an animal study; for completion of the study; and for submission of the final study report to FDA. In addition, FDA recognizes that some study commitments include an agreement to report important intermediate timepoints or early study endpoints (e.g., evaluation of surrogate endpoints in a study also measuring clinical benefit). If a study commitment includes reporting at such intermediate timepoints, these timepoints should be included in the projected schedule submitted under §§ 314.81(b)(2)(vii)(a)(7) and 601.70(b)(7).

FDA is requiring that the schedule in this section include actual dates, if they represent milestones that have already been reached, in addition to projected dates. This is particularly appropriate for studies that were started before the effective date of this final rule and for which a particular aspect of the study has already been completed by the effective date. Actual dates are also appropriate if a particular aspect of the study (e.g., submission of study protocol) was completed prior to approval of the drug or agreement on the postmarketing commitment.

The agency is revising the section title “Schedule for conduct, completion and reporting of the postmarketing study commitment” by removing the word “conduct” from the section heading. FDA is making this revision because the word “conduct” is not necessary.

FDA is modifying the section “Current status of the postmarketing study commitment” at §§ 314.81(b)(2)(vii)(a)(8) and 601.70(b)(8), by removing from the paragraph “Ongoing” the requirement to include the date the study was completed, and removing from the paragraph “Submitted” the requirement to provide the date the final study report was submitted to FDA. These date requirements have been added to the section “Explanation of the study’s status” at §§ 314.81(b)(2)(vii)(a)(9) and 601.70(b)(9) to consolidate under this section all information providing clarification of the status of individual studies. The paragraph “Pending” has been clarified to state that studies that have not been initiated will be categorized as delayed if the study is behind the original schedule for completion and reporting of the postmarketing commitment. FDA is modifying the paragraph “Terminated” to clarify that this category is to be used if a study has been terminated before completion, but a final study report has not yet been submitted to the agency.

FDA is requiring, as proposed, that annual status reports include the applicant’s name, product name, application (NDA, ANDA, BLA, and supplement) number, date of postmarketing commitment, and the product approval date. However, in §§ 314.81(b)(2)(vii)(a)(4) and 601.70(b)(4), the agency is replacing the “Date of product’s U.S. approval” section heading with the heading “Date of U.S. approval of NDA, ANDA, or BLA.” This change is being made to clarify identification of the postmarketing commitment because the product may be included in more than one application.

FDA is keeping all other sections of the status reports as proposed, because the agency believes that the information that is being requested in them is necessary to identify a postmarketing study commitment, to establish the progress of a postmarketing study commitment, or to identify the reasons for the failure of the applicant to conduct the study. The agency will use these status reports to review the progress of postmarketing study commitments and to meet its statutory reporting obligations (i.e., its report to Congress on this topic by October 1, 2001, and its annual report in the **Federal Register** on the status of postmarketing study commitments). FDA anticipates

that preparation of a status report for a postmarketing study commitment will not be burdensome. Each status report should contain no more than one page of information that is readily available to the applicant.

(Comment 2) One comment said that much of the information required to be submitted in an NDA annual report under the proposed rule must already be submitted to an investigational new drug application (IND). The comment noted that the risk of duplicative reporting burdens is exacerbated by the fact that NDA and IND anniversary dates may differ and applicants may be required to collect and reconcile information for the same postmarketing studies twice a year. The comment recommended that FDA scale back the scope of the information required to be submitted to the NDA annual report and also permit applicants to reference pertinent sections of an IND and IND annual report in an NDA annual report.

FDA declines to permit applicants to reference their IND and IND annual reports in the status report section of NDA and BLA annual reports. Most of the information contained in these reports is different from the information submitted to the IND and is used by the agency for different purposes. FDA needs the information that is contained in a status report in the prescribed format to meet its statutory reporting obligations. FDA does not believe that preparation of status reports will be unduly burdensome for applicants, and the fact that no comments were submitted on the information collection provisions supports this conclusion.

B. Public Disclosure of Information

New §§ 314.81(b)(2)(vii)(b) and 601.70(e) require the agency to publicly disclose any information concerning a postmarketing study if the agency determines that the information is necessary to identify the applicant or to establish the status of the study, including the reasons, if any, for failure to conduct, complete, and report the study. The proposal stated that information necessary to establish the status of a postmarketing study would include the study protocol, patient accrual rates, reports of unexpected suspected adverse drug reactions, and study results. The proposal also specified that FDA would not publicly disclose trade secrets, as defined in § 20.61

(21 CFR 20.61), or information, described in § 20.63 (21 CFR 20.63), the disclosure of which would constitute an unwarranted invasion of personal privacy.

(Comment 3) Three comments strongly objected to the public disclosure provisions of the proposed rule contending that such disclosure could potentially result in release of confidential and highly sensitive commercial information. One comment said that the “proposed rule directly violates the limits set by FDAMA,” when the proposed rule calls for the disclosure of the study protocol, patient accrual rates, reports of unexpected suspected adverse drug reactions, and study results. The comment claimed that the agency is incorrect when it asserts that this additional information is “necessary to identify the applicant and to establish the status of a study.” Another comment noted that there is an inconsistency in the content of the status reports section and the public disclosure sections of the proposed rule that needs clarification. The content of the status report section is limited to patient accrual and study status, whereas the public disclosure section states that the study protocol and study results will be made public.

The comments recommended that study protocols, reports of unexpected suspected adverse drug reactions, and results of the study not be publicly disclosed. One comment said that clinical protocols are highly proprietary in terms of design and analytical plan and that applicants should only be required to provide a general description of the study for public disclosure. Another comment said that with regard to disclosure of study results in an orphan drug exclusivity situation, the publication of detailed study results may allow competitors to strategically redesign clinical trials in an effort to nullify another company’s market exclusivity. The comment also said that detailed knowledge of study results could also lead to potential disputes between competitors via negative advertising. The comment recommended that applicants only be required to provide a brief summary of the study results for public disclosure. Another comment said that disclosure of study results represents bad science because it is generally not appropriate to “peek” at results from a study before its scheduled completion. Another comment said that annual public disclosure of all reports of unexpected adverse drug reactions are inappropriate for epidemiological studies

because no scientifically-based conclusions can be drawn when safety reports are reviewed out of context of the study population and without regard to the appropriate controls. However, the comment noted that if any new association is established between a product and a previously unknown adverse reaction, such information should be made public. Another comment noted that if a study is delayed because of low patient accrual rates, despite legitimate efforts to enroll subjects, information posted on a website could negatively affect the company and its ability to complete the commitment.

FDA has considered these comments and agrees that disclosure of the study protocol, reports of unexpected suspected adverse drug reactions, and the results of studies reported under §§ 314.81(b)(2)(vii) and 601.70 are not necessary to achieve the purposes of the rule or section 130 of FDAMA. Section 130 of FDAMA requires the agency to publicly disclose information pertaining to status reports if that information is necessary to identify the applicant and to establish the status of a study, including the reasons, if any, for failure to conduct, complete, and report the study. FDA has, therefore, decided to remove the following sentence from proposed §§ 314.81(b)(2)(vii)(b) and 601.70(e): “Information necessary to establish the status of a postmarketing study includes the study protocol, patient accrual rates, reports of unexpected suspected adverse drug reactions, and study results.”

For purposes of public disclosure, the agency intends to release information that establishes the status of a study and that is contained in §§ 314.81(b)(2)(vii)(a)(1) through (b)(2)(vii)(a)(9) and 601.70(b)(1) through (b)(9) of the final rule. These sections do not call for study results and FDA does not believe that any information provided by applicants in these sections of a status report would be considered confidential commercial information. However, even if an applicant considers certain information in these sections to be confidential commercial information, section 130(a) of FDAMA would authorize FDA to release such information if it were necessary to identify the applicant or to establish the status of a study, including the reasons, if any, for failure to conduct, complete, and report the study. The agency has decided that a study protocol, study results,

and reports of unexpected suspected adverse drug reactions are not information necessary to establish the status of the study. However, the agency expects to continue to receive study protocols and study results since that information is necessary for FDA to determine whether a study commitment has been satisfied. The agency also expects to continue to receive reports of unexpected suspected adverse drug reactions, which are required reports. Other laws, such as the Freedom of Information Act (FOIA), would determine whether the agency would release to the public study protocols, study results, and reports of unexpected suspected adverse drug reactions.

FDA believes that the number of patients who are enrolled in a postmarketing study is an important factor establishing the status of a study. Applicants would provide such information to FDA in status reports, and, under section 130 of FDAMA, patient accrual rates would be considered to be public information.

(Comment 4) One comment claimed that the proposed rule is contrary to FOIA and the Trade Secrets Act. The comment said that FOIA specifically exempts confidential commercial information from public disclosure under 5 U.S.C. 552(b)(4) (so-called “FOIA Exemption 4”) and that the Trade Secrets Act makes it a crime for a Federal employee to disclose any information within the scope of FOIA Exemption 4, including confidential commercial information to the extent that the disclosure is not authorized by law (18 U.S.C. 1905). The comment further asserted that there is nothing in the legislative history of FDAMA to suggest that Congress intended to make public information that would otherwise be exempt from disclosure under FOIA, except to the very narrow extent necessary to identify a sponsor and establish the status of a study. The comment said that the only information that should be required to be disclosed should be basic information to identify the study and sponsor, and the standardized information on the status of a study (or, if applicable, a brief explanation of why a study was not conducted). The comment said that this is the only information that should be posted on FDA’s website.

FDA disagrees with the comment because it does not believe that status reports would contain confidential commercial information. In any event, section 130(a) of FDAMA requires the agency

to disclose certain information from postmarketing study reports even if that information ordinarily would be considered confidential commercial information. Since section 130(a) of FDAMA requires disclosure, the disclosure would be authorized by law and not prohibited by the Trade Secrets Act. FDA will not disclose any information from postmarketing study reports that is considered a trade secret as defined in § 20.61(a) and section 301(j) of the act (21 U.S.C. 331(j)) or would constitute an unwarranted invasion of personal privacy as defined in § 20.63.

(Comment 5) Two comments wanted to know what information would be disclosed on FDA's website and what format would be used for this purpose. One of the comments asked if a company would have the opportunity to review information before it is posted on the website to ensure that confidential data are not disclosed. Another comment requested that an efficient procedure be established to identify the information that is disclosable. The comment said that applicants should be instructed to include a section in their postmarketing status reports that is specifically intended for public disclosure. The comment noted that this approach is consistent with that adopted recently by FDA for information provided by sponsors to advisory committees in connection with open advisory committee meetings. The comment also noted that if FDA disagrees with an applicant's designation of disclosable information, the agency could then consult with the applicant.

FDA intends to include information on its webpage that is provided to FDA by applicants in their status reports. In the proposed rule, FDA stated that the website will contain, at a minimum, the following information for each postmarketing study commitment: Name of the applicant, application number, product name, dosage form, product use category, type of study, commitment description, commitment date, projected study completion date, current status of commitment, applicant summary of status, annual report due date, and date annual report received. At this time, FDA intends to include this information on FDA's webpage, as well as the date the final study report is received by the agency. In the future, FDA may decide to add or remove types of information from the website or to revise the format. FDA intends to provide a suggested format for postmarketing reports and an example of what information will appear on the agency website

in the guidance the agency is developing or on which the agency will solicit public comment. (See section I.C of this document.)

With regard to the submission of a publicly releasable version of the status report by applicants, the agency will not require such submissions at this time. FDA is considering recommending, in guidance, that applicants include with their status reports a publicly releasable version of the report. This version of the status report would facilitate FDA's transmission of information to its website.

(Comment 6) One comment said that the agency needs to clarify that public disclosure does not apply to chemistry, manufacturing, and controls (CMC) studies. Another comment said that the agency needs to clarify that public disclosure does not apply to the log of outstanding regulatory business section of approved NDA annual reports.

The rule has been clarified to require the status of CMC studies that the applicant has agreed to conduct to be reported under § 314.81(b)(2)(viii). FDA would not publicly disclose in its annual **Federal Register** report or website information concerning postmarketing study commitments submitted in NDA annual reports under §§ 314.81(b)(2)(viii) and 314.81(b)(2)(ix). FDA intends to limit information in the annual **Federal Register** report and website to information submitted in status reports under §§ 314.81(b)(2)(vii) and 601.70.

C. Scope of Proposed Rule—FDAMA 130 Studies for Drug and Licensed Biological Products

Annual reports submitted under § 314.81(b)(2) apply to human drug products with an approved NDA or ANDA. New § 601.70 applies to human licensed biological products that meet the definition of “drug” under the act; it would not apply to biological products that meet the definition of “medical device” under the act. Revised § 314.81(b)(2)(vii) and new § 601.70 require, under section 130 of FDAMA, status reports of postmarketing studies concerning clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology that are required by FDA (e.g., accelerated approval clinical benefit studies and pediatric studies) or that the applicant committed to conduct, in writing, either at the time of approval of an application for the drug product or

licensed biological product or of a supplement to an application, or after approval of an application or a supplement.

(Comment 7) One comment requested that reporting on the status of nonclinical studies (e.g., preclinical) be made optional for § 601.70.

FDA disagrees with the comment. The agency is requiring that information be provided for postmarketing nonclinical toxicology studies because of their significance in assessing the safety of drug and licensed biological products.

(Comment 8) One comment said that FDA should set some reasonable limit on how far back in time it will require applicants to report on studies that they committed to conduct years before enactment of section 130 of FDAMA but that still remain open. The comment suggested that the agency could remove the status report requirement for a study commitment that was entered into more than 3 years ago.

FDA disagrees with the comment. Section 130 of FDAMA requires that the status of postmarketing study commitments, whether entered into before or after the date of enactment of FDAMA, be reported to FDA annually until the commitment is completed or terminated. Many clinical studies take several years to complete. Studies that applicants committed to conduct several years ago are only now coming to completion and will yield important information about the safety and effective use of the drug or biological product. The agency will monitor an applicant's submission of status reports under §§ 314.81(b)(2)(vii) and 601.70 for any postmarketing study commitment that the agency has formally tracked in agency postmarketing commitment data bases.

D. Scope of Proposed Rule—Other Studies for Drug Products

In § 314.81(b)(2)(viii), FDA proposed to require that status reports be submitted for any postmarketing study not included under § 314.81(b)(2)(vii) that is being performed by, or on behalf of, the applicant. The applicant was to provide the information prescribed under § 314.81(b)(2)(vii) for each of the postmarketing studies subject to reporting.

(Comment 9) Three comments requested that the agency remove this section from the regulations because section 130 of FDAMA only requires status reports for studies that a company has committed to FDA to perform. One of the comments said that, as an alternative, the agency could limit the studies in this section to those which the applicant committed to FDA that it would conduct.

FDA disagrees with the comment. The agency currently requires that the status of any postmarketing studies performed by, or on behalf of, the applicant be provided in NDA annual reports and FDA will continue to require status reports for these studies. It was not the intent of this rule, however, to expand current reporting requirements for postmarketing studies reported under § 314.81(b)(2)(viii). In considering the comments received, FDA has decided that it is not necessary to prescribe the content and format for status reports under § 314.81(b)(2)(viii) and has removed this requirement. Section 314.81(b)(2)(viii) and (b)(2)(ix) are retained in this rule due to the reorganization of § 314.81(b)(2)(vii).

(Comment 10) Two comments requested that CMC studies be exempt from inclusion in proposed § 314.81(b)(2)(viii) because there is no purpose in providing such information in this section. One comment said that even though current § 314.81(b)(2)(vii) requires status reports for “any” postmarketing study, existing regulation and guidance have previously established a more narrow definition of the CMC reporting requirement. The comment explained that current § 314.81(b)(2)(iv) states that reports for CMC changes are only required for new information that may affect FDA’s previous conclusions about the safety or effectiveness of the drug product and that the guidance for industry on “Format and Content for the CMC section of an Annual Report” specifies only the need to include stability data under current § 314.81(b)(2)(vii). The comment recommended that CMC study information be provided under current § 314.81(b)(2)(iv) so that all the information pertinent to the chemistry review would be consolidated into a single section. Another comment said that reporting the status of CMC studies is not pertinent and repeating this information under proposed § 314.81(b)(2)(viii) is redundant and unnecessary.

FDA disagrees in part with this comment. Section 314.81(b)(2)(vii) currently requires reporting of any postmarketing study. FDA's current guidance for industry states that data accumulated from ongoing stability studies should be included in § 314.81(b)(2)(vii). Therefore, it is clear from existing regulations and guidance that stability studies are to be reported under existing § 314.81(b)(2)(vii) (now § 314.81(b)(2)(viii) of the rule). These reports provide FDA with valuable information regarding the safety and efficacy of products, and FDA has decided to retain this requirement in the final rule. However, FDA has decided to modify § 314.81(b)(2)(viii) to clarify the reporting requirements for CMC studies. FDA will maintain a requirement for reporting data from all ongoing product stability studies including those that are being conducted without a postmarketing study commitment, (e.g., annual stability assessment performed in conformance with 21 CFR 211.166). For other types of CMC studies, FDA is revising § 314.81(b)(2)(viii) to require a status report for only those studies which the applicant has agreed to perform. This section now reads as follows:

Status of other postmarketing studies. A status report of any postmarketing study not included under paragraph (b)(2)(vii) of this section that is being performed by, or on behalf of, the applicant. A status report is to be included for any chemistry, manufacturing, and controls studies that the applicant has agreed to perform and for all product stability studies.

Information from other CMC studies, experiences, investigations, or tests that are not stability studies or the subject of a specific commitment but that provide new information that may affect FDA's previous decisions about product safety and efficacy will continue to be reported under § 314.81(b)(2)(iv).

E. Fulfillment of Commitments

FDA proposed at §§ 314.81(b)(2)(vii) and 601.70(b) that the status of postmarketing studies be submitted to the agency annually until FDA notifies the applicant, in writing, that the agency concurs with the applicant's determination that the study commitment has been fulfilled or that the study is either no longer feasible or would no longer provide useful information.

(Comment 11) Three comments requested that FDA specify the timeframe for agency review of a final study report and for notifying the applicant whether or not the postmarketing study commitment has been fulfilled or that a commitment is either no longer feasible to fulfill or would no longer provide useful information. One of the comments suggested a 90-day timeframe and another comment suggested a 60-day timeframe.

In general, FDA expects that final study reports for postmarketing study commitments will be submitted to the agency with a supplemental application to modify a product's labeling when the studies support such a change. When they are submitted in support of a supplement, FDA will review the submission under established review times for supplements. (For Prescription Drug User Fee Act (PDUFA) products, see letters from Secretary of Health and Human Services to the Chairman of the Committee on Commerce of the House of Representatives (143 Congressional Record H10886, November 13, 1997), and the Chairman of the Committee on Labor and Human Resources of the Senate (143 Congressional Record S12653, November 13, 1997)). If no supplemental application is submitted or a supplement is submitted for a product not covered by PDUFA, FDA will generally review the final study report and notify the applicant in writing within 1 year of receipt of the report regarding whether it considers the commitment to have been met.

(Comment 12) One comment said that the requirement to continue to submit status reports on terminated postmarketing studies until FDA considers that the study commitments have been fulfilled is too vague. The comment requested clarification of the criteria that the agency would use to deem a study fulfilled.

FDA will review final study reports and determine whether or not the study met the objectives of the commitment. Whether or not the objectives have been met will have to be determined on a case-by-case basis because of the variety of postmarketing study commitments. Once FDA completes its review of the final study report, it will notify the applicant, in writing, of the agency's conclusion. An applicant would be required to submit annual status reports to FDA until it receives

written notification that the agency concludes that: (1) The study commitment has been met, or (2) the study is either no longer feasible or would no longer provide useful information.

FDA may conclude that the study is no longer feasible but that the commitment's objectives remain important and can be addressed through a study of modified design. In this case, the original study may be terminated with no further reporting once a new postmarketing study commitment and schedule are agreed upon.

FDA may conclude that even though a study was completed, it failed to meet the commitment objectives; or an applicant may terminate a study that FDA subsequently determines is feasible and would yield useful information. In these cases, the agency may ask the applicant to undertake another study to fulfill its commitment.

(Comment 13) One comment said that FDA's confirmation in writing that a study commitment has been fulfilled could reasonably be accommodated through addition of a suitable field in the Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use), which would be completed by FDA at the time that receipt of the annual report is acknowledged. From that point on, the comment said that the status of the postmarketing commitment should be tracked under outstanding regulatory business. The comment noted that this suggestion, intended to reduce the administrative burden on FDA of acknowledging receipt of final study reports, would not remove the need for FDA to confirm in writing that they have evaluated the study report and concur with the applicant's conclusions or proposed action (e.g., submission and approval of a labeling supplement to accommodate study results).

FDA disagrees with this suggestion. The agency will not acknowledge that the postmarketing study commitment has been fulfilled until it has reviewed the final study report and concurs that the commitment has been met. Applicants found to have fulfilled their commitments will be notified in writing. In addition, this information will be acknowledged in the agency's data bases and website.

F. Annual Report Submission Date

Current § 314.81(b)(2) requires that an applicant submit an annual report each year within 60 days of the anniversary date of U.S. approval of the application. FDA proposed to require the same submission times at § 601.70(c) for annual progress reports of postmarketing study commitments entered into by applicants with licensed biological products.

(Comment 14) One comment said that, for postmarketing studies that are already underway and for which annual reports are already provided, applicants should be permitted to continue to use the annual reporting cycles that are already established. The comment noted that it submits annual reports based on the anniversary date of the study initiation rather than the anniversary date of U.S. approval.

Current § 314.81(b)(2) requires that NDA annual reports be submitted to the agency within 60 days of the anniversary date of approval of the application. FDA will continue to require that NDA annual reports be submitted within the same timeframe. Applicants would not be permitted to submit NDA or BLA annual reports based on the anniversary date of a study's initiation.

Many drug and licensed biological products have multiple postmarketing studies underway that were initiated on different dates. The submission of annual reports based on the date of study initiation would result in multiple reports in any given year, thereby unnecessarily increasing an applicant's reporting burden and complicating FDA's tracking and review of postmarketing study commitment reports. It is FDA's intent to minimize the reporting burden on industry by requiring only a single annual report for any NDA, ANDA, or BLA product. This single report allows applicants to submit status information on all studies and allows FDA reviewers to review and evaluate at one time the progress of all studies, some of which may be related.

G. Implementation Scheme—Effective Dates

FDA proposed that any final rule that may issue based on the proposed rule become effective 90 days after its date of publication in the **Federal Register**. Applicants that have entered into a commitment prior to November 21, 1997, to conduct a postmarketing study under proposed

§ 314.81(b)(2)(vii) or § 601.70 would be required, as mandated by FDAMA, to submit an initial report to FDA within 6 months after the effective date of any final rule that issued based on the proposed rule.

(Comment 15) One comment requested that FDA provide that the effective date of any final rule be 120 days after the date of publication of the rule in the **Federal Register**. The comment noted that, with the proposed 90-day effective date, an applicant could be required to submit an initial report 5 months following publication of the final rule, depending on the anniversary date of their products. The comment claimed that the 90-day effective date is not consistent with section 130 of FDAMA which indicates that applicants should have 6 months following the issuance of final regulations to submit initial reports on postmarketing study commitments. The comment recommended that the effective date be modified to ensure that all applicants will have at least 6 months to file reports under the new requirements.

FDA does not believe that section 130 of FDAMA requires the agency to give a period of 6 months after issuing a final rule for applicants to prepare a postmarketing study status report. Rather, section 130(a) of FDAMA requires all applicants, regardless of the anniversary date of the approval of their drug, to submit status information for postmarketing study commitments made prior to November 21, 1997, within 6 months of the final rule's issuance. This timely submission of information is necessary to allow FDA to meet its reporting obligation in providing Congress with an evaluation of industry's performance in meeting postmarketing commitment obligations and FDA's performance in reviewing those postmarketing study reports.

However, FDA has considered the comment and is revising the effective date to 120 days after the date of publication of the rule in the **Federal Register**. Although FDA anticipates the information required to complete an initial report on the progress of postmarketing studies is readily available to the applicant, the agency understands that some applicants may have a greater reporting burden than other applicants due to a larger number of postmarketing commitments. Revision of the effective date will give all applicants a minimum of 4 months to prepare an initial report

on their postmarketing commitments. If an applicant chooses to submit the report up to 60 days after the anniversary date of the approval of the drug, the applicant will have 6 months in which to file an initial report.

Once the rule goes into effect, annual reports due on or after the effective date must meet the format and content requirements of this final rule. An applicant who has annual reports due on or after [*insert date 6 months after the effective date of this rule*], will be required to submit a special 6-month report for all commitments made prior to November 21, 1997. This one-time additional report is required if:

- (1) The drug or biological product was approved before November 21, 1997;
- (2) Postmarketing study commitments were made before November 21, 1997; and
- (3) The next annual report is not due until [*insert date 6 months after the effective date of this final rule*], or later.

(Comment 16) One comment requested that FDA remove the requirement to submit a separate initial report within 6 months of the effective date of the final rule for pre-FDAMA commitments. The comment asserted that these reports would contain data from a time interval of less than 1 year and that significant resources would be required to prepare such a report as well as for FDA to review the report, which, due to the limited data, would be of minimal value. Another comment said that there is little value in requiring submission of these separate reports and that the requirement should be fulfilled in the next annual report due for each product. The comment claimed that this would also be more compatible with collation and publication of the planned Annual Federal Register Report.

FDA does not accept this suggestion. Section 130(a) of FDAMA requires that an initial report on the progress of postmarketing commitments made prior to November 21, 1997, be submitted to FDA within 6 months of the agency issuing a final rule. Although some information on postmarketing studies may be included in annual reports for new drugs submitted before the effective date of the final rule, these reports may not include all information necessary for FDA

to evaluate a study's progress. Also, applicants of approved biological products may not have previously submitted study status information. FDA acknowledges that the special 6-month report may contain limited new data. However, the submission of that data, in the format required by §§ 314.81(b)(2)(vii) and 601.70(b), is necessary to allow FDA to respond in a timely manner to Congress as required in section 130(b) of FDAMA. Therefore, FDA maintains this one-time reporting requirement.

IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

FDA has examined the impact of this final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1966 (Public Law 104–121)), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to analyze whether a rule may have a significant impact on a substantial number of small entities and, if it does, to analyze regulatory options that would minimize the impact. Section 202 of the Unfunded Mandates Reform Act requires that agencies prepare a written statement of anticipated costs and benefits and before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector of \$100 million (adjusted annually for inflation) in any one year.

The agency has determined that the final rule is not a significant action as defined in the Unfunded Mandates Reform Act, and will not have an effect on the economy that exceeds \$100 million in any one year. The analysis below details FDA's estimate of the potential cost and the potential benefit of the rule. Based on FDA's analysis using available data, the agency does not anticipate that the rule will result in a significant impact on a substantial number of small entities.

A. Nature of Impact

Currently, applicants holding approved NDA's or ANDA's are required to submit annual reports to the agency that include information on the current status of any postmarketing studies of the drug product performed by, or on the behalf of, the applicant. Although the final rule prescribes the format for the required information, this requirement would add no new economic burden for the majority of NDA and ANDA applicants. About half of the applicants holding approved NDA's or ANDA's with outstanding postmarketing study commitments made prior to the enactment of FDAMA may incur a small cost the first year, if their annual report is due within the last 6 months after the effective date of issuance of the final rule and they must submit one initial report within the first 6 months after the effective date. FDA estimates that: (1) There will be approximately 116 such reports submitted; (2) each report will report on two postmarketing studies, on average; and (3) each report will require about 16 hours (or 8 hours per study) to complete. Assuming an average wage rate of \$35 per hour, the estimated, one-time cost of this provision is \$64,960.

Applicants with licensed biological products are currently required to submit information on postmarketing studies in pediatric populations in annual reports to the agency. These applicants will incur additional costs to comply with the requirements in this final rule. The agency estimates that about 33 applicants will submit postmarketing status reports (reporting on two postmarketing studies, on average) on approximately 43 approved BLA's annually. As the reporting requirements are not extensive and the information is readily accessible to the applicant, FDA estimates that establishments will require about 16 hours to complete the required information for each report

(or 8 hours for each study). Assuming an average wage rate of \$35 per hour, the estimated incremental cost of the annual reporting requirement will be \$560 per report, for an industry total of \$24,080 per year. As with applicants holding NDA's or ANDA's, a few applicants with licensed biological products with outstanding postmarketing study commitments may also incur an additional, one-time cost because they must submit their initial report within the first 6 months after the effective date of the final rule and an annual report within the last 6 months of the year. FDA estimates there will be approximately seven such reports, for a total one-time cost of about \$4,000.

B. Small Business Impacts

The requirements in this final rule will not have a significant economic impact on a substantial number of small entities. The agency neither expects the final rule to result in an increased number of completed postmarketing studies nor believes that applicants will incur significantly increased costs from completing studies earlier than intended, as a result of the reporting, tracking, and disclosure activities implemented by the agency. Because affected applicants holding NDA's and ANDA's must currently submit annual reports to the agency, they already have procedures in place to monitor their postmarketing studies. The additional reporting requirement for applicants holding approved BLA's and the reformatting of the annual reports for applicants holding NDA's and ANDA's would be minimal. To simplify the reporting requirement further, however, the agency will publish a guidance for industry to aid applicants in preparing reports in the proper format (see section I.C of this document).

C. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government.

Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

VI. The Paperwork Reduction Act of 1995

This final rule contains information collection provisions that were reviewed by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520), and that FDA invited the public to send comments to OMB. No comments were received by OMB on these provisions. A description of these provisions is shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Reporting the Status of Postmarketing Studies for Approved Human Drugs and Licensed Biological Products.

Description: Section 506B of the act provides FDA with additional authority for monitoring the progress of postmarketing studies that companies have made a commitment to conduct and also requires the agency to make the status of these studies publicly available.

Under section 506B(a) of the act, applicants that have committed to conduct a postmarketing study for an approved human drug or biological product must submit to FDA a report of the progress of the study or the reasons for the failure of the applicant to conduct the study. This report must be submitted within 1 year after the U.S. approval of the application and then annually until the study is completed or terminated. Under §§ 314.81(b)(2)(vii) and 601.70(b), information submitted in a status report would be limited to that which is needed to sufficiently identify each applicant that has committed to conduct a postmarketing study, the status of the study that is being reported, and the reasons, if any, for the applicant's failure to conduct, complete, and report the study.

Currently under § 314.81(b)(2), applicants holding an NDA or an ANDA must submit status reports on postmarketing studies for the approved human drug product as part of an annual report to FDA. The agency is amending § 314.81(b)(2)(vii) to specify information that must be included in status reports submitted under section 506B of the act (studies of clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology that are required by FDA or that an applicant commits, in writing, to conduct either at the time of approval of an application or a supplement to an application or after approval of an application or supplement). New § 314.81(b)(2)(viii) of the final rule requires status information on any postmarketing study commitments not reported under paragraph (b)(2)(vii) that are being performed by, or on behalf of, the applicant; and paragraph (b)(2)(ix) permits the applicant to list any open regulatory business with FDA concerning the drug product subject to the application. For licensed biological products, FDA is requiring applicants under § 601.70 to submit postmarketing status reports for studies of clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology that are required by FDA or that an applicant of a BLA commits to conduct, in writing, at the time of approval of an application or a supplement to an application or after approval of an application or a supplement. FDA is revising § 601.28(c) to require that the status of postmarketing pediatric studies described in new § 601.70 be reported under § 601.70 rather than § 601.28. This final rule is intended to provide FDA with specific procedures for monitoring the progress of postmarketing studies that companies have made a commitment, in writing, to conduct and also to permit the agency to make the status of these studies publicly available.

Description of Respondents: Applicants holding approved applications for human drugs and biological products that have committed to conduct postmarketing studies.

As required by section 3506(c)(2)(B) of the PRA, FDA provided an opportunity for public comment on the information collection requirements of the proposed rule (64 FR 67207). In accordance with the PRA, OMB reserved approval of the information collection burden in the proposed rule stating “FDA shall assess comments received regarding information collection

requirements contained in the proposed rule. These comments shall be addressed in the preamble to the final rule.” No letters of comment on the information collection requirements were submitted to OMB.

Under current § 314.81(b)(2), applicants with approved NDA’s and ANDA’s for human drugs are required to submit to the agency two copies of the annual reports that must include information on the current status of any postmarketing study (OMB control No. 0910-0001).

New § 314.81(b)(2)(vii) expressly requires status information to be provided in a specific format as part of the status reports of postmarketing study commitments (clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology), a subpart of the annual report. Based on past experience, the agency estimates that each applicant holding an approved NDA or ANDA would expend an additional 8 hours to reformat the annual report. This is a one-time burden required under new § 314.81(b)(2)(vii). Based on the number of drug applicants in past years who have committed to conduct postmarketing studies, the agency estimates that this provision would apply to approximately 183 applicants and approximately 462 postmarketing studies.

Based upon information obtained from the Center for Biologics Evaluation and Research’s computerized application and license tracking data base, the agency estimates that approximately 33 applicants with 43 approved BLA’s have committed to conduct approximately 86 postmarketing studies (clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology) and would be required to submit an annual progress report on those postmarketing studies under § 601.70. Section 601.70 requires postmarketing studies status reports for the first time for all biological products. Previously, status reports were required only for postmarketing studies in pediatric populations. Based on past experience with reporting under § 314.81(b)(2), the agency estimates that approximately 8 hours annually are required for an applicant to gather, complete, and submit the appropriate information for each study (approximately two studies per report). Included in these 8 hours is the time necessary to initially format the status report.

Applicants holding NDA's, ANDA's, and BLA's whose anniversary date of U.S. approval of the application falls within the latter half of the year after the effective date of this final rule are required under section 506B of the act to submit an initial report to FDA for postmarketing studies committed to be conducted prior to November 21, 1997, within 6 months after the effective date of the final rule in addition to the reports required by the final rule. This information collection is a statutory requirement for which the final rule adds no additional burden other than prescribing the format. The burden of setting up the format is calculated under §§ 314.81(b)(2)(vii) and 601.70(b).

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN¹

21 CFR Section	No. of Respondents	Annually Frequency per Response	Total Annual Response	Hours per Response	Total Hours
314.81(b)(2)(vii), (b)(2)(viii), and (b)(2)(ix) ²	183	2.5	462	8	3,696
601.70(b) and (d)	33	2.6	86	8	688
Total					4,384

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

²One-time burden for reformatting annual report.

The information collection requirements of the final rule have been submitted to OMB for review. Prior to the effective date of the final rule, FDA will publish a document in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection requirements in the final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

List of Subjects

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 314 and 601 are amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

1. The authority citation for 21 CFR part 314 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 356, 356a, 356b, 356c, 371, 374, 379e.

2. Section 314.81 is amended by revising the introductory text of paragraph (b)(2), by revising paragraph (b)(2)(vii), and by adding paragraphs (b)(2)(viii) and (b)(2)(ix) to read as follows:

§ 314.81 Other postmarketing reports.

* * * *

(b) * * *

(2) *Annual report.* The applicant shall submit each year within 60 days of the anniversary date of U.S. approval of the application, two copies of the report to the FDA division responsible for reviewing the application. Each annual report is required to be accompanied by a completed transmittal Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use), and must include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval that ends on the U.S. anniversary date. The report is required to contain in the order listed:

* * * *

(vii) *Status reports of postmarketing study commitments.* A status report of each postmarketing study of the drug product concerning clinical safety, clinical efficacy, clinical pharmacology, and nonclinical toxicology that is required by FDA (e.g., accelerated approval clinical benefit studies, pediatric studies) or that the applicant has committed, in writing, to conduct either at the time of approval of an application for the drug product or a supplement to an application, or after

approval of the application or a supplement. For pediatric studies, the status report shall include a statement indicating whether postmarketing clinical studies in pediatric populations were required by FDA under § 201.23 of this chapter. The status of these postmarketing studies shall be reported annually until FDA notifies the applicant, in writing, that the agency concurs with the applicant's determination that the study commitment has been fulfilled or that the study is either no longer feasible or would no longer provide useful information.

(a) *Content of status report.* The following information must be provided for each postmarketing study reported under this paragraph:

(1) *Applicant's name.*

(2) *Product name.* Include the approved drug product's established name and proprietary name, if any.

(3) *NDA, ANDA, and supplement number.*

(4) *Date of U.S. approval of NDA or ANDA.*

(5) *Date of postmarketing study commitment.*

(6) *Description of postmarketing study commitment.* The description must include sufficient information to uniquely describe the study. This information may include the purpose of the study, the type of study, the patient population addressed by the study and the indication(s) and dosage(s) that are to be studied.

(7) *Schedule for completion and reporting of the postmarketing study commitment.* The schedule should include the actual or projected dates for submission of the study protocol to FDA, completion of patient accrual or initiation of an animal study, completion of the study, submission of the final study report to FDA, and any additional milestones or submissions for which projected dates were specified as part of the commitment. In addition, it should include a revised schedule, as appropriate. If the schedule has been previously revised, provide both the original schedule and the most recent, previously submitted revision.

(8) *Current status of the postmarketing study commitment.* The status of each postmarketing study should be categorized using one of the following terms that describes the study's status on the anniversary date of U.S. approval of the application or other agreed upon date:

(i) *Pending.* The study has not been initiated, but does not meet the criterion for delayed.

(ii) *Ongoing.* The study is proceeding according to or ahead of the original schedule described under paragraph (b)(2)(vii)(a)(7) of this section.

(iii) *Delayed.* The study is behind the original schedule described under paragraph (b)(2)(vii)(a)(7) of this section.

(iv) *Terminated.* The study was ended before completion but a final study report has not been submitted to FDA.

(v) *Submitted.* The study has been completed or terminated and a final study report has been submitted to FDA.

(9) *Explanation of the study's status.* Provide a brief description of the status of the study, including the patient accrual rate (expressed by providing the number of patients or subjects enrolled to date, and the total planned enrollment), and an explanation of the study's status identified under paragraph (b)(2)(vii)(a)(8) of this section. If the study has been completed, include the date the study was completed and the date the final study report was submitted to FDA, as applicable. Provide a revised schedule, as well as the reason(s) for the revision, if the schedule under paragraph (b)(2)(vii)(a)(7) of this section has changed since the last report.

(b) *Public disclosure of information.* Except for the information described in this paragraph, FDA may publicly disclose any information described in paragraph (b)(2)(vii) of this section, concerning a postmarketing study, if the agency determines that the information is necessary to identify the applicant or to establish the status of the study, including the reasons, if any, for failure to conduct, complete, and report the study. Under this section, FDA will not publicly disclose trade secrets, as defined in § 20.61 of this chapter, or information, described in § 20.63

of this chapter, the disclosure of which would constitute an unwarranted invasion of personal privacy.

(viii) *Status of other postmarketing studies.* A status report of any postmarketing study not included under paragraph (b)(2)(vii) of this section that is being performed by, or on behalf of, the applicant. A status report is to be included for any chemistry, manufacturing, and controls studies that the applicant has agreed to perform and for all product stability studies.

(ix) *Log of outstanding regulatory business.* To facilitate communications between FDA and the applicant, the report may, at the applicant's discretion, also contain a list of any open regulatory business with FDA concerning the drug product subject to the application (e.g., a list of the applicant's unanswered correspondence with the agency, a list of the agency's unanswered correspondence with the applicant).

PART 601—LICENSING

3. The authority citation for 21 CFR part 601 is revised to read as follows:

Authority: 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

4. Section 601.28 is amended by revising the second sentence in paragraph (c) to read as follows:

§ 601.28 Annual reports of postmarketing pediatric studies.

* * * * *

(c) * * * The statement shall include whether postmarketing clinical studies in pediatric populations were required or agreed to, and, if so, the status of these studies shall be reported to FDA in annual progress reports of postmarketing studies under § 601.70 rather than under this section.

5. Subpart G, consisting of § 601.70, is added to part 601 to read as follows:

Subpart G—Postmarketing Studies**§ 601.70 Annual progress reports of postmarketing studies.**

(a) *General requirements.* This section applies to all required postmarketing studies (e.g., accelerated approval clinical benefit studies, pediatric studies) and postmarketing studies that an applicant has committed, in writing, to conduct either at the time of approval of an application or a supplement to an application, or after approval of an application or a supplement.

Postmarketing studies within the meaning of this section are those that concern:

- (1) Clinical safety;
- (2) Clinical efficacy;
- (3) Clinical pharmacology; and
- (4) Nonclinical toxicology.

(b) *What to report.* Each applicant of a licensed biological product shall submit a report to FDA on the status of postmarketing studies for each approved product application. The status of these postmarketing studies shall be reported annually until FDA notifies the applicant, in writing, that the agency concurs with the applicant's determination that the study commitment has been fulfilled, or that the study is either no longer feasible or would no longer provide useful information. Each annual progress report shall be accompanied by a completed transmittal Form FDA-2252, and shall include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval which ends on the U.S. anniversary date. The report must provide the following information for each postmarketing study:

- (1) *Applicant's name.*
- (2) *Product name.* Include the approved product's proper name and the proprietary name, if any.
- (3) *Biologics license application (BLA) and supplement number.*
- (4) *Date of U.S. approval of BLA.*
- (5) *Date of postmarketing study commitment.*

(6) *Description of postmarketing study commitment.* The description must include sufficient information to uniquely describe the study. This information may include the purpose of the study, the type of study, the patient population addressed by the study and the indication(s) and dosage(s) that are to be studied.

(7) *Schedule for completion and reporting of the postmarketing study commitment.* The schedule should include the actual or projected dates for submission of the study protocol to FDA, completion of patient accrual or initiation of an animal study, completion of the study, submission of the final study report to FDA, and any additional milestones or submissions for which projected dates were specified as part of the commitment. In addition, it should include a revised schedule, as appropriate. If the schedule has been previously revised, provide both the original schedule and the most recent, previously submitted revision.

(8) *Current status of the postmarketing study commitment.* The status of each postmarketing study should be categorized using one of the following terms that describes the study's status on the anniversary date of U.S. approval of the application or other agreed upon date:

(i) *Pending.* The study has not been initiated, but does not meet the criterion for delayed.

(ii) *Ongoing.* The study is proceeding according to or ahead of the original schedule described under paragraph (b)(7) of this section.

(iii) *Delayed.* The study is behind the original schedule described under paragraph (b)(7) of this section.

(iv) *Terminated.* The study was ended before completion but a final study report has not been submitted to FDA.

(v) *Submitted.* The study has been completed or terminated and a final study report has been submitted to FDA.

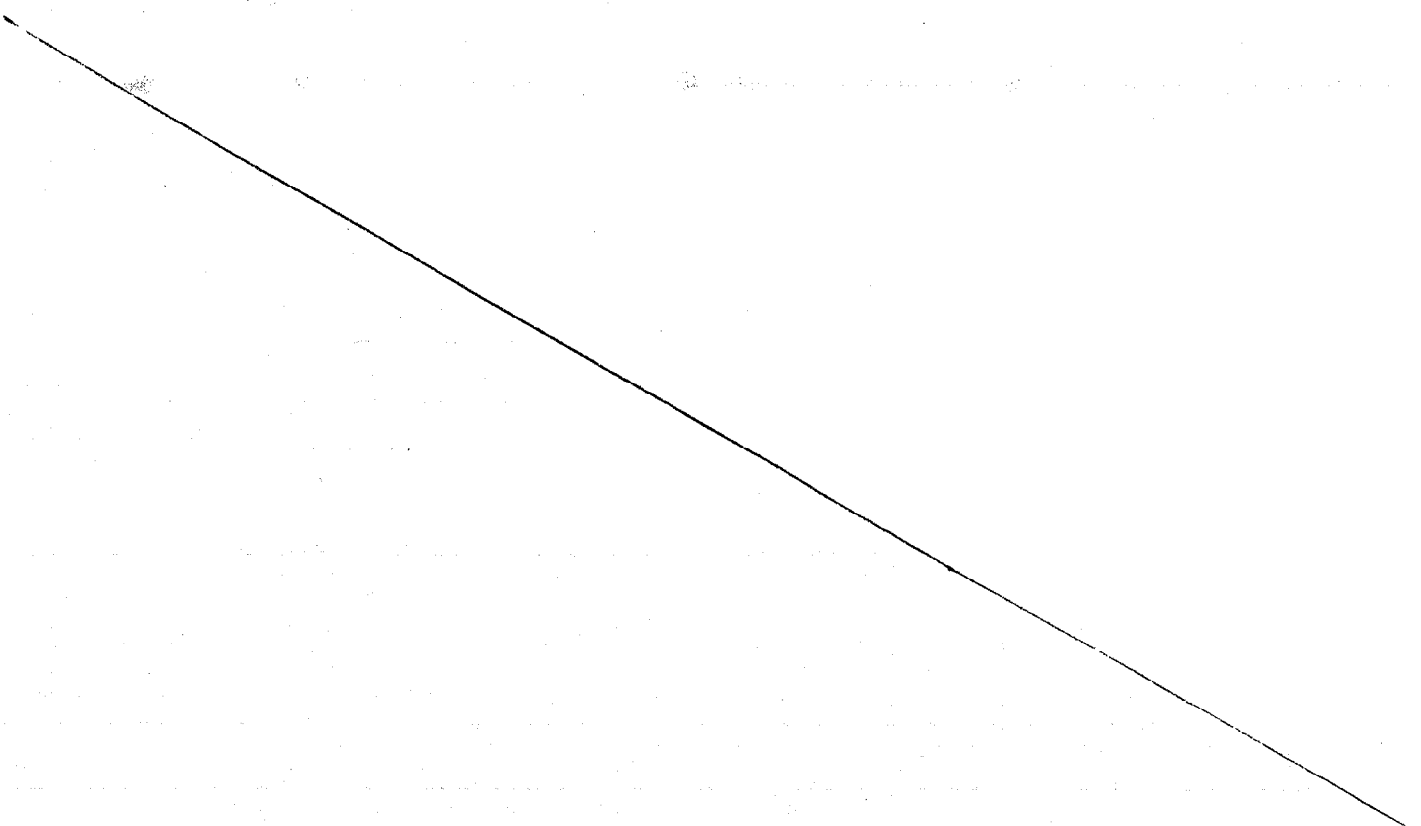
(9) *Explanation of the study's status.* Provide a brief description of the status of the study, including the patient accrual rate (expressed by providing the number of patients or subjects enrolled to date, and the total planned enrollment), and an explanation of the study's status identified under paragraph (b)(8) of this section. If the study has been completed, include the date

the study was completed and the date the final study report was submitted to FDA, as applicable. Provide a revised schedule, as well as the reason(s) for the revision, if the schedule under paragraph (b)(7) of this section has changed since the previous report.

(c) *When to report.* Annual progress reports for postmarketing study commitments entered into by applicants shall be reported to FDA within 60 days of the anniversary date of the U.S. approval of the application for the product.

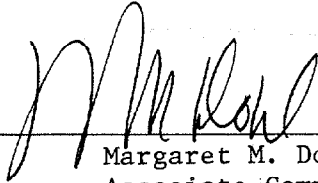
(d) *Where to report.* Submit two copies of the annual progress report of postmarketing studies to the Food and Drug Administration, Center for Biologics Evaluations and Research, Document Control Center (HFM-99), 1401 Rockville Pike, Rockville, MD 20852-1448.

(e) *Public disclosure of information.* Except for the information described in this paragraph, FDA may publicly disclose any information concerning a postmarketing study, within the meaning of this section, if the agency determines that the information is necessary to identify an applicant or to establish the status of the study including the reasons, if any, for failure to conduct, complete, and report the study. Under this section, FDA will not publicly disclose trade secrets, as defined



in § 20.61 of this chapter, or information, described in § 20.63 of this chapter, the disclosure of which would constitute an unwarranted invasion of personal privacy.

Dated: 10/13/00
October 13, 2000



Margaret M. Dotzel,
Associate Commissioner for Policy.

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